



US 20030203960A1

(19) **United States**

(12) **Patent Application Publication**
Hausheer

(10) **Pub. No.: US 2003/0203960 A1**

(43) **Pub. Date: Oct. 30, 2003**

(54) **DRUGS FOR PROPHYLAXIS OR
MITIGATION OF TAXANE-INDUCED
NEUROTOXICITY**

Publication Classification

(51) **Int. Cl.⁷ A61K 31/337; A61K 31/255**

(52) **U.S. Cl. 514/449; 514/517**

(76) Inventor: **Frederick H. Hausheer**, Boerne, TX
(US)

(57) **ABSTRACT**

Correspondence Address:

Thomas J. Dodd
BioNumerik Pharmaceuticals, Inc.
Suite 1250
8122 Datapoint Drive
San Antonio, TX 78229 (US)

Provided are pharmaceutical drugs for preventing or mitigating adverse actions associated with taxane antineoplastic drugs which are frequently and widely used in cancer chemotherapy, and pharmaceutical compositions which allow us to shorten the duration of treatment with taxane antineoplastic agents and/or to repeat the taxane treatment course more times, as well as drugs suitable for the therapeutic schedules.

(21) Appl. No.: **10/135,975**

(22) Filed: **Apr. 30, 2002**

DRUGS FOR PROPHYLAXIS OR MITIGATION OF TAXANE-INDUCED NEUROTOXICITY

FIELD OF THE INVENTION

[0001] The present invention relates to drugs that are useful for prophylaxis and mitigation of taxane-induced disorders of peripheral nervous systems, and pharmaceutical compositions for increasing the dosage and/or shortening the duration or schedule of treatment with taxane antineoplastic agents.

BACKGROUND OF THE INVENTION

[0002] Many anticancer agents used in chemotherapy are known to cause various undesirable toxicities associated with their cytotoxic properties. It is widely known that there are many instances where such undesirable or intolerable drug related toxicities impose crucial limitations on the dose and schedule for administration of such antineoplastic agents to patients with cancer. It is notable to consider that the drug induced toxicity associated with many cancer chemotherapy drugs can offset the potential benefit to the patient undergoing treatment since the development of chemotherapy induced toxicity can result in delaying treatment, or in severe cases, lead to the discontinuance of treatment altogether. These two outcomes can allow the patient's cancer to progress unchecked or to limit the opportunity to cure or significantly palliate the patient's disease by limiting the dose, duration or schedule of chemotherapy treatments that are aimed at curing or palliating the patient's cancer.

[0003] It is well known that such antineoplastic agent-induced toxicities vary with antineoplastic agent species or class that are well recognized by experts. Furthermore, adverse events or toxicities produced by such anticancer drugs are based on a diversity of biochemical and pharmacological mechanisms that may be entirely different from one another even though superficially, the patient's symptoms and signs are apparently identical or similar in terms of the nature of their description. Therefore, it is also known that it is not necessarily a reasonable expectation to prevent or to mitigate all such undesirable toxicities associated with all chemotherapy agents or to inhibit their side effects non-selectively. Drug related side effects occur in vivo upon administration of a specific antineoplastic agent based on the toxicities common to that antineoplastic agent, and observed patient side-effect symptoms vary according to diverse factors and sensitive natures per in vivo tissue, cell or organ and the interaction with other drugs that are administered. Accordingly, the safe and effective means for solving such problems will vary. Of course, it is important to recognize that an ideal chemoprotective agent is one that would not result in an additional separate or additive toxicity to the patient in conjunction with the administration of chemotherapy; this is one of the novel objects of the current invention.

[0004] Representatives of taxane antineoplastic agents are paclitaxel, docetaxel, and others currently in clinical and pre-clinical development. Such taxane antineoplastic agents have been frequently and widely employed to treat patients with breast cancer as well as patients with ovarian, lung, bladder, esophagus, and other sites of origin in the United States, Europe Japan and other countries. However, the administration of taxanes requires precautions because seri-

ous and potentially life threatening side effects often occur. In particular, the clinical use of taxanes is frequently delayed or discontinued altogether due to toxicities causing the disorder of peripheral nerve systems (including peripheral neuropathy) such as numbness in the extremities, paresthesias, weakness, paralysis, arthralgia, myalgia, as well as others. In these instances the taxane medication treatment must be suspended, the dose of taxane chemotherapy reduced, or in the more severe cases, it is discontinued because of the neurotoxicity. Halting treatment or altering the dosage of the taxane may be detrimental to the patient's chances of long term survival or control of the cancer, since it is well known that the delay, reduction in dose or the discontinuance of chemotherapy allows the unopposed progression of the patient's cancer. Therefore, a safe and effective solution for preventing or reducing the likelihood of such common and clinically important problems relating to chemotherapy induced neurotoxicity is eagerly demanded since it is estimated that approximately 60% of patients receiving taxane chemotherapy can develop drug induced neurotoxicity.

[0005] Up to the present, various attempts have been attempted to mitigate, but not prevent the toxicities of antineoplastic agents. It is notable that there is no currently approved drug therapy that has been demonstrated in patients to be safe and effective in preventing taxane induced neurotoxicity. The treating physician basically has three treatment options: 1) delay treatment until the toxicity resolves to an acceptable level; 2) reduce the dose of taxane chemotherapy; and 3) discontinue treatment with the taxane altogether. The treating physician can employ any combination of 1 and 2 together and option 3 is reserved for more severe cases of taxane neurotoxicity. A variety of new approaches to prevent or mitigate taxane-induced neurotoxicity have been pursued more recently.

[0006] Representatives of platinum analogue antineoplastic drugs include cisplatin, carboplatin, oxaliplatin, and others in both clinical and preclinical development. Like the taxanes and many other antineoplastic drugs, platinum analogue antineoplastic drugs are associated with a number of toxicities, including nephrotoxicity, bone marrow suppression, neurotoxicity, and others.

[0007] The present inventors have filed patent applications disclosing the use of 2,2'-dithiobis ethane sulfonate and other dithioethers in order to alleviate cisplatin induced toxicity, i.e., nephrotoxicity (U.S. Pat. Nos. 5,789,000; 5,866,169; 5,866,615; 5,866,617; 5,902,610 and others . . . JP, A, 10-509143 (1998)) and carboplatin induced toxicity, i.e., myelosuppression, and also vomiting (U.S. Pat. No. 6,037,336; JP, A, 2001-500872 (2001)). The present inventors have also pointed out that 2,2'-dithiobis ethane sulfonate and dithioethers are applicable to mitigation of toxicities mediated by various antineoplastic agents (U.S. Pat. Nos. 5,919,816; 6,025,488; 6,040,294; 6,040,304; 6,040,312; 6,043,249; 6,046,159; 6,046,234; 6,048,849; 6,057,361; 6,066,645; and 6,066,668; WO 99/20264).

[0008] In the above WO 99/20264 and U.S. Pat. No. 5,919,816, a very broad range is disclosed for dose rates of dithioethers to taxane antineoplastic agents, i.e., the weight-to-weight ratio of taxane antineoplastic agent to dithioethers is from 1:4 to 1:4,000 for parenteral administration routes; however, with regard to dithioethers, the optimum dosage

for use in humans has not been fully determined and is expected to be highly variable because of the wide variability of doses and schedules of chemotherapy agents that are used alone and in combination with different treatment regimens for cancer patients.

[0009] The process for synthesizing the dithioethers is outlined in U.S. Pat. No. 5,808,160 and others.

SUMMARY OF THE INVENTION

[0010] Under such circumstances, the present inventors have carried out an intensive study for 2,2'-dithiobis ethane sulfonate among the dithioethers. As a result, the present inventors have discovered that pharmaceutical preparations comprising 2,2'-dithiobis ethane sulfonate, also known as dimesna and/or BNP7787, (either as the disodium salt or as a free acid) particularly certain dosages of 2,2'-dithiobis ethane sulfonate, allow for (1) the substantially safe and effective prevention as well as mitigation of the aforementioned taxane antineoplastic agent related neurotoxicity, in particular, paresthesias in peripheral nerve systems; (2) the more effective duration of treatment with taxane antineoplastic agents by preventing treatment delays, taxane dosage reductions and discontinuance of chemotherapy secondary to neurotoxicity; and (3) this invention allows the safe and effective administration of many more than the average number of cycles of antineoplastic drug medication than previously possible. As a result of our research we also believe that it will be possible to increase the dosage of chemotherapy as well without additional toxicity and that this may result in substantially improved patient benefit from such treatment. The evidence of patient benefit from this present invention is clearly manifested by two patients who would not be expected to experience a complete disappearance of their cancer (one of these patients has a probable metastatic non-small cell lung cancer to the brain and has been in a complete remission for more than one year and the other patient has a cholangiocarcinoma that has undergone complete remission in less than 3 months of taxane based chemotherapy. In addition, many other patients receiving this novel chemoprotectant in combination with taxane-based chemotherapy have experienced major antitumor responses that have lasted for months. None of any of these patients has experienced severe taxane induced neurotoxicity, including patients who have received up to 9 chemotherapy cycles of treatment. Based on further investigation, the inventors have succeeded in completing the present invention.

[0011] The present invention relates to effective amounts of dithioether drugs for preventing or mitigating taxane antineoplastic agent-induced neurotoxicity, more specifically the taxane antineoplastic agent-induced toxic paresthetic disorder of peripheral nerve systems.

[0012] The present invention relates to disulfide chemoprotectant admixed pharmaceutical compositions and drugs for coadministration with taxane antineoplastic agents which enable us to shorten the duration of treatment with taxane antineoplastic agents, and/or to repeat the taxane antineoplastic agent medication course more times than ever. This invention also teaches a new and useful method to prevent taxane treatment delays, treatment discontinuance, and to allow chemotherapy dose increases as well as to shorten the infusional/administration time for patients.

[0013] The present invention further relates to disulfide containing chemoprotective agents that are administered as mixtures or in combination with taxane chemotherapy agents for the purpose of preventing taxane agent-induced disorders and toxicity to the peripheral nerve systems, more specifically the taxane antineoplastic agent-induced sensory and motor disorders of peripheral nerve systems. The present invention also involves the co-formulation or co-administration of disulfide containing chemoprotective drugs in combination with taxane drugs which allow the physician to prevent or reduce the probability of taxane treatment delays, taxane dose reductions, discontinuance of taxane chemotherapy, and also to permit the physician to shorten the infusional time for taxane treatment with said antineoplastic agents, and/or to increase the dose of the antineoplastic agent and/or to repeat the antineoplastic agent medication course more times, in connection with not only taxanes alone but also in combination with platinum analogue antineoplastic drug coadministration therapy. All of these benefits relate to the prevention or mitigation of taxane-induced neurotoxicity by this invention as well as to allow more aggressive chemotherapy treatment to be given without greater toxicity to the patient.

[0014] The present invention also relates to 2,2'-dithiobis ethane sulfonate-admixed pharmaceutical compositions and drugs, which enable the physician to safely and effectively co-administer taxane antineoplastic agents in combination with platinum analogue antineoplastic agents, prevent or reduce the probability of taxane treatment delays, taxane dose reductions, discontinuance of taxane chemotherapy to shorten the duration of treatment with said antineoplastic agents, and/or to increase the dose of the antineoplastic agent and/or to repeat the antineoplastic agent medication course more times. All of the foregoing benefits relate to the prevention or mitigation of taxane and platinum induced neurotoxicity by this invention.

[0015] The present invention also relates to drugs for preventing or mitigating the taxane antineoplastic agent-mediated disorder of peripheral nerve systems, more specifically the taxane antineoplastic agent-mediated sensory and/or motor disorders of peripheral nerve systems, which contain 2,2'-dithiobis ethane sulfonate or a disulfide at a specific admixture amount per total pharmaceutical preparation.

[0016] The present invention also relates to novel pharmaceutical compositions and drugs for coadministration with taxane antineoplastic agents that contain a specific amount of chemoprotectant and enable the physician to prevent or reduce the probability of taxane treatment delays, taxane dose reductions, discontinuance of taxane chemotherapy resulting from taxane induced neurotoxicity, and to allow the physician to shorten the infusional administration treatment with taxane antineoplastic agents and/or to safely allow the physician and patient to receive more courses of chemotherapy as well as to allow dose escalation of chemotherapy that would otherwise not be achievable without the use of the instant invention. The present invention further relates to drugs which comprise a specific amount of disulfide chemoprotectant and to prevent or mitigate the taxane antineoplastic agent-induced disorder of peripheral nerve systems, more specifically the taxane antineoplastic agent-induced sensory or motor disorder of peripheral nerve systems, and/or drugs which comprise a specific amount of

disulfide chemoprotectant and allow the physician to prevent or reduce the probability of taxane treatment delays, taxane dose reductions, discontinuance of taxane chemotherapy, to shorten the duration of treatment with said antineoplastic agents, and/or to repeat the antineoplastic agent medication treatment for more courses, and/or in higher doses, in connection with not only taxane but also platinum analogue antineoplastic drug coadministration therapy.

[0017] The present invention also relates to pharmaceutical compositions and drugs that comprise a specified amount of 2,2'-dithiobis ethane sulfonate and enable us to co-administer taxane antineoplastic agents in combination with platinum analogue antineoplastic agents, to shorten the duration of treatment with said antineoplastic agents, and/or to repeat the antineoplastic agent medication course more times, with possible dose escalation of the antineoplastic agent. The present invention also relates to pharmaceutical preparations wherein the disulfide chemoprotectant is admixed or used together at a specific amount or concentration in solution to 1 part by weight, molar ratio or concentration of taxane antineoplastic agents.

[0018] In another aspect, the present invention provides pharmaceutical drugs, pharmaceutical compositions, drug sets, therapeutic measures or methods, therapeutic schedules, packs suitable for taxane antineoplastic therapy (including therapy in combination with platinum analogue antineoplastic drugs), and the like, which comprise disulfide chemoprotectants in any of preferred forms for preventing or mitigating the said taxane antineoplastic agent-related adverse actions in fields of said therapy.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

[0019] Specific embodiments of the present invention are listed as follows:

[0020] 1) a drug for mitigating or preventing taxane antineoplastic agent-induced or -mediated disorder of peripheral nerve systems, which comprises an effective amount of disulfide chemoprotectant;

[0021] 2) a drug for preventing mitigating the taxane antineoplastic agent-induced sensory or motor disorder of peripheral nerve systems, which comprises an effective amount of disulfide chemotherapy;

[0022] 1. administration of a disulfide chemoprotectant that enables the physician to shorten the infusional administration period of taxanes—thereby allowing for greater patient convenience and lower hospital costs;

[0023] 2. administration of a disulfide chemoprotectant that enables the physician to reduce the probability of taxane induced neurotoxicity leading to treatment delays, treatment discontinuance, and to allow higher doses and/or shorter intervals of taxane therapy to be administered to cancer patients.

[0024] 3. administration of a disulfide chemoprotectant to a cancer patient with or without mild to moderate neurotoxicity from any cause (diabetes, alcoholic, other drug induced—e.g., ethambutol, dilantin, vincristine, tegretol, epothilone, etc. neu-

ropathies, nutritional neuropathy, and the like, that would allow the affected patient to receive taxane based chemotherapy that would not otherwise be contraindicated due to the presence of a pre-existing neuropathy

[0025] 3) a drug for shortening the infusion period and or the interval of treatment with a taxane antineoplastic agent in taxane antineoplastic therapy, which comprises an effective amount of 2,2'-dithiobis ethane sulfonate.

[0026] 4) this may allow administration of chemotherapy to a patient for more than one year.

[0027] 5) Molar ratios would be BNP7787: taxane of 50:1 to as high as 2000:1.

[0028] 4) the drug according to the above 3) in which the duration of treatment consists of a specified period for medication of a taxane antineoplastic agent and an interval for suspending taxane antineoplastic agent medication.

[0029] 5) the drug according to the above 4) in which the duration of treatment comprises at least 3 continuous courses wherein each course consists of a specified period for medication of a taxane antineoplastic agent and an interval for suspending taxane antineoplastic agent medication;

[0030] 6) a drug for shortening an interval for suspending the medication of a taxane antineoplastic agent (or an interval intervening to next taxane antineoplastic agent medication in order to temporarily halt taxane antineoplastic agent administration) in taxane antineoplastic therapy, which comprises an effective amount of 2,2'-dithiobis ethane sulfonate;

[0031] 7) the drug according to any of the above 4) to 6) in which the interval for administering the taxane antineoplastic agent medication is from 1 day to 4 weeks;

[0032] 8) the drug according to any of the above 4) to 6) in which the interval for administering the taxane antineoplastic agent medication is from 1 day to 2 weeks;

[0033] 9) the drug according to any of the above 4) to 6) in which the interval for administering the taxane antineoplastic agent medication is from 1 day to 1.5 weeks;

[0034] 10) the drug according to any of the above 4) to 6) in which the interval for administering the taxane antineoplastic agent medication is from 1 day to 1.0 weeks;

[0035] 11) a drug for increasing the number of courses for treatment with a taxane antineoplastic agent (or a course number wherein each course is comprised of one taxane antineoplastic agent medication period and one interval for administering the taxane antineoplastic agent medication) in taxane antineoplastic therapy, which comprises an effective amount of 2,2'-dithiobis ethane sulfonate;

- [0036] 12) the drug according to the above 11) in which the taxane treatment comprises 2 or more treatment courses;
- [0037] 13) the drug according to the above 11) in which the taxane treatment comprises 5 or more courses;
- [0038] 14) the drug according to the above 11) in which the taxane treatment comprises 6 or more courses;
- [0039] 15) the drug according to the above 11) in which the taxane treatment comprises 7 or more courses;
- [0040] 16) the drug according to the above 11) in which the taxane treatment comprises 8 or more courses;
- [0041] 17) the drug according to the above 11) in which the taxane treatment comprises 9 or more courses;
- [0042] 18) the drug according to any of the above 11) to 17), in which said courses are continuous;
- [0043] 19) a drug for mitigating taxane antineoplastic agent-related adverse actions which comprises plural or all members selected from elements as set forth in any of the above 1) to 18);
- [0044] 20) the drug according to any of the above 1) to 19) in which 2,2'-dithiobis ethane sulfonate is admixed at 5 to 70 wt % per total pharmaceutical preparation;
- [0045] 21) the drug according to any of the above 1) to 19) in which 2,2'-dithiobis ethane sulfonate is admixed at 10 to 50 wt %;
- [0046] 22) the drug according to any of the above 1) to 21) in which the amount of admixed 2,2'-dithiobis ethane sulfonate is for administering 4.1 g/m² to 80.0 g/m² (body surface area) per dose;
- [0047] 23) the drug according to any of the above 1) to 22) which is for intravenous or oral administration routes;
- [0048] 24) the drug according to the above 23) in which the drug for intravenous or oral administration routes is in any of solution or suspension in liquid form, freeze-dried and solid forms;
- [0049] 25) the drug according to any of the above 1) to 24) in which the taxane antineoplastic agent is paclitaxel;
- [0050] 26) the drug according to any of the above 1) to 24) in which the taxane antineoplastic agent is docetaxel;
- [0051] 27) the drug according to any of the above 1) to 26) which is for taxane antineoplastic drug therapy in combination with platinum analogue antineoplastic drug therapy;
- [0052] 28) the drug according to the above 27) in which the platinum analogue antineoplastic agent is cisplatin;
- [0053] 29) the drug according to the above 27) in which the platinum analogue antineoplastic agent is carboplatin;
- [0054] 30) a pharmaceutical composition for coadministration with a taxane antineoplastic agent, which comprises an effective amount of 2,2'-dithiobis ethane sulfonate in order to mitigate the taxane antineoplastic agent-induced disorder of peripheral nerve systems;
- [0055] 31) a pharmaceutical composition for coadministration with a taxane antineoplastic agent, which comprises an effective amount of 2,2'-dithiobis ethane sulfonate in order to mitigate the taxane antineoplastic agent-induced paresthetic disorder of peripheral nerve systems;
- [0056] 32) a pharmaceutical composition for coadministration with a taxane antineoplastic agent, which comprises an effective amount of 2,2'-dithiobis ethane sulfonate in order to shorten the duration of treatment with the taxane antineoplastic agent in taxane antineoplastic therapy;
- [0057] 33) a pharmaceutical composition for coadministration with a taxane antineoplastic agent, which comprises an effective amount of 2,2'-dithiobis ethane sulfonate in order to shorten an interval for administering medication with the taxane antineoplastic agent in any taxane containing antineoplastic therapy;
- [0058] 34) a pharmaceutical composition for coadministration with a taxane antineoplastic agent, which comprises an effective amount of 2,2'-dithiobis ethane sulfonate in order to increase the number of courses of treatment with a taxane antineoplastic agent in taxane antineoplastic therapy;
- [0059] 35) a pharmaceutical composition for coadministration with a taxane antineoplastic agent, which comprises an effective amount of 2,2'-dithiobis ethane sulfonate in order to exert plural or all actions selected from the group consisting of
- [0060] 1. a mitigating activity against the taxane antineoplastic agent-related disorder of peripheral nerve systems,
- [0061] 2. a mitigating activity against the taxane antineoplastic agent-related paresthetic disorder of peripheral nerve systems,
- [0062] 3. a shortening of the duration of taxane antineoplastic agent treatment,
- [0063] 4. a shortened time interval for administering taxane antineoplastic agent medication during taxane antineoplastic drug therapy, and
- [0064] 5. an increasing activity on the number of courses for taxane antineoplastic agent medication during taxane antineoplastic drug therapy;
- [0065] 36) the pharmaceutical composition according to any of the above 30) to 35) in which 2,2'-dithiobis ethane sulfonate is admixed at 5 to: >70 wt % per total pharmaceutical preparation;

- [0066] 37) the pharmaceutical composition according to any of the above 30) to 35) in which 2,2'-dithiobis ethane sulfonate is admixed at 0.10 to 50 wt %;
- [0067] 38) the pharmaceutical composition according to any of the above 30) to 35) in which the amount of admixed 2,2'-dithiobis ethane sulfonate is for administrating 4.1 to 80.0 g/m² (body surface area) per dose;
- [0068] 39) the pharmaceutical composition according to any of the above 30) to 38) which is for intravenous or oral administration routes;
- [0069] 40) the pharmaceutical composition according to the above 39) in which the drug for intravenous or oral administration routes is in any of liquid, freeze-dried and solid forms;
- [0070] 41) the pharmaceutical composition according to any of the above 30) to 40) in which the taxane antineoplastic agent is paclitaxel;
- [0071] 42) the pharmaceutical composition according to any of the above 30) to 40) in which the taxane antineoplastic agent is docetaxel;
- [0072] 43) the pharmaceutical composition according to any of the above 30) to 42) which is for taxane antineoplastic drug therapy in combination with platinum analogue antineoplastic drug therapy;
- [0073] 44) the pharmaceutical composition according to the above 43) in which the platinum analogue antineoplastic agent is cisplatin;
- [0074] 45) the pharmaceutical composition according to the above 43) in which the platinum analogue antineoplastic agent is carboplatin;
- [0075] 46) a drug comprising an effective amount of 2,2'-dithiobis ethane sulfonate for coadministration with a taxane antineoplastic agent in a form of packs or formulations in order to allow the following:
- [0076] (1) one course is set to include the following administration schedules: the taxane antineoplastic agent is administered once a day wherein the antineoplastic agent is administered at 1 day to 5 week intervals, and 2,2'-dithiobis ethane sulfonate is administered on the same date as the antineoplastic agent is administered, and
- [0077] (2) the medication is repeated for at least 4 courses, preferably 7 or more courses;
- [0078] 47) the drug according to the above 46) in which the weight ratio of 2,2'-dithiobis ethane sulfonate to antineoplastic agent is from 1:10 to 1:2500;
- [0079] 48) the drug according to the above 46) in which the dose of 2,2'-dithiobis ethane sulfonate is from 4.1 to 80.0 g/m² (body surface area);
- [0080] 49) the drug according to any of the above 46.) to 48) in which the single dose of the taxane antineoplastic agent is from 60 to 300 mg/m² (body surface area) per day for paclitaxel or from 30 to 240 mg/m² (body surface area) per day for docetaxel;
- [0081] 50) the drug according to any of the above 46) to 49) in which the course is repeated at least 8 or more times;
- [0082] 51) the drug according to any of the above 46) to 50) in which the antineoplastic agents are administered at intervals of (a) one day to 4 weeks, (b) one day to 3 weeks, or (c) one day to 2 weeks;
- [0083] 52) the drug according to any of the above 46) to 50) in which the antineoplastic agent is administered at an interval of one day to 1.5 weeks;
- [0084] 53) the drug according to any of the above 46) to 52) which exerts at least one, plural or all actions selected from the group consisting of
- [0085] (1) a mitigating activity against the taxane antineoplastic agent-related disorder of peripheral nerve systems,
- [0086] (2) a mitigating activity against the taxane antineoplastic agent-related paresthetic disorder of peripheral nerve systems,
- [0087] (3) a shortening activity on the duration of taxane antineoplastic agent treatment,
- [0088] (4) a shortening activity on the interval for suspending taxane antineoplastic agent medication during taxane antineoplastic drug therapy, and
- [0089] (5) an increasing activity on the number of courses for taxane antineoplastic agent medication during taxane antineoplastic drug therapy;
- [0090] 54) a drug comprising an effective amount, of 2,2'-dithiobis ethane sulfonate for coadministration with a taxane antineoplastic agent in a form of packs or formulations in order to allow the following:
- [0091] (1) one course is set to include the following administration schedules:
- [0092] the taxane antineoplastic agent is administered once per day as well as a platinum analogue antineoplastic agent is administered on the same date as the taxane antineoplastic agent is administered wherein the antineoplastic agents are administered at one day to 6 week intervals, and 2,2'-dithiobis ethane sulfonate is administered on the same date as the antineoplastic agents are administered, and
- [0093] (2) the medication is repeated for at least 4 courses, preferably 7 or more courses;
- [0094] 55) the drug according to the above 54) in which the weight ratio of 2,2'-dithiobis ethane sulfonate to taxane antineoplastic agent is from 1:10 to 1:2500.
- [0095] 56) the drug according to the above 54) in which the dose of 2,2'-dithiobis ethane sulfonate is from 4.1 to 80.0 g/m² (body surface area);
- [0096] 57) the drug according to any of the above 54) to 56) in which the single dose of the taxane antineoplastic agent is from 60 to 300 mg/m² (body surface area) per day for paclitaxel or from 30 to 240 mg/m² (body surface area) per day for docetaxel;

- [0097] 58) the drug according to any of the above 54) to 56) in which the platinum analogue antineoplastic agent is cisplatin or carboplatin;
- [0098] 59) the drug according to any of the above 54) to 58) in which the course is repeated at least 8 or more times;
- [0099] 60) the drug according to any 61) to 59) in which the antineoplastic agents are administered at intervals of (a) one day to 5 weeks, (b) one day to 4 weeks or (c) one day to 3 weeks;
- [0100] 61) the drug according to any of the above 54) to 59) in which the antineoplastic agent is administered at an interval of 2.5 to 5 weeks;
- [0101] 62) the drug according to any of the above 54) to 61) which exerts at least one, plural or all actions selected from the group consisting of
- [0102] (1) a mitigating activity against the taxane antineoplastic agent-related disorder of peripheral nerve system,
- [0103] (2) a mitigating activity against the taxane antineoplastic agent-related paresthetic disorder of peripheral nerve system,
- [0104] (3) a shortening activity on the duration of taxane antineoplastic agent treatment,
- [0105] (4) a shortening activity on the interval for suspending taxane antineoplastic agent medication during taxane antineoplastic drug therapy, and
- [0106] (5) an increasing activity
- [0107] 63) the drug according to any of the above 46) to 62) which serves as an agent for mitigating taxane antineoplastic agent-related adverse actions;
- [0108] 64) the pharmaceutical composition according to any of the above 30) to 45) in which 2,2'-dithiobis ethane sulfonate is co-administrable as a medication set in combination with taxane antineoplastic agent medication;
- [0109] 65) the pharmaceutical composition according to 64) in which a platinum analogue antineoplastic agent is co-administrable as a medication set; and
- [0110] The aforementioned taxane antineoplastic agent includes paclitaxel, docetaxel and derivatives and analogues thereof. Among them, paclitaxel and docetaxel have been already approved and marketed as pharmaceutical drugs, and other taxanes are in clinical and preclinical development.
- [0111] The aforementioned platinum analogue antineoplastic agents include cisplatin, carboplatin and other platinum derivatives. Among them, cisplatin and carboplatin have been already approved and marketed as pharmaceutical drugs, and other platinum agents are in various stages of clinical and preclinical development.
- [0112] The aforementioned 2,2'-dithiobis ethane sulfonate is a known compound, *J. Org. Chem.*, 26, 1330 (1961); *J. Org. Chem.*, 59, 8239 (1994); etc., and can be manufactured by methods as described in those known documents or according to techniques similar thereto or as described in the United States patents referred to, supra. Alternatively, 2,2'-dithiobis ethane sulfonate can also be manufactured by a method disclosed in JP, A, 2001-501219 (2001).
- [0113] The present invention provides pharmaceutical drug for preventing or mitigating the taxane anticancer drug-related disorder of peripheral nerve systems (including peripheral neuropathy), which comprises an effective amount of 2,2'-dithiobis ethane sulfonate. Particularly, the present invention provides embodiments for a pharmaceutical drug for preventing or mitigating the taxane anticancer drug-related paresthetic disorder of peripheral nerve systems (including peripheral neuropathic paresthesia) in relation to taxane drug therapy, which comprises an effective amount of 2,2'-dithiobis ethane sulfonate.
- [0114] In an embodiment, the present invention provides a drug for mitigating the taxane anticancer drug-related disorder of peripheral nerve systems which contains 2,2'-dithiobis ethane sulfonate at a dose of a specific wt %. The percent amount of admixed 2,2'-dithiobis ethane sulfonate is preferably from 5% to 70 wt %, and more, preferably from 10% to 50 wt % per total pharmaceutical preparation.
- [0115] When a taxane antineoplastic agent is administered, the disorder of peripheral nerve systems (e.g., peripheral neuropathy) is said to most frequently occur as an adverse effect and its onset rate is more than 60% in patients who receive taxane based chemotherapy. The taxane antineoplastic agent-related disorder of peripheral nerve systems (e.g., peripheral neuropathy) may include main symptoms such as paresthesia (an abnormal sensation, such as numbness, tingling, burning, distal anesthesia, etc.) in relation to the limbs. The drug for mitigating the taxane anticancer drug-mediated disorder can prevent or alleviate such disorders of peripheral nerve systems, including numbness, pain and the like in the limbs.
- [0116] The mitigating and suppressing (or inhibiting) efficacy of 2,2'-dithiobis ethane sulfonate on the aforementioned taxane antineoplastic agent-mediated disorder of peripheral nerve systems is supported by Examples, which are set forth below.
- [0117] The dosage forms of the aforementioned drugs or pharmaceutical compositions are not limited to, but include any as long as they are suitable for achieving the objectives of the present invention. Dosage is preferably by intravenous or oral administration route.
- [0118] Thus, a taxane antineoplastic agent may be usually administered intravenously while the inventive drugs and pharmaceutical compositions may be in any of dosage forms, i.e., intravenous formulations wherein the administration route is identical with that for the taxane antineoplastic agent or oral formulations wherein the administration route is different from a taxane dosage route.
- [0119] The above-mentioned drugs or pharmaceutical compositions for intravenous or oral administration routes may be in any of liquid, freeze-dried and solid forms as mentioned below. Usually, each dosage form as aforementioned can be manufactured by admixing 2,2'-dithiobis ethane sulfonate with one or more members selected from pharmaceutically acceptable additives (hereinafter also referred to "pharmaceutical ingredients).
- [0120] For example, the intravenous formulation contains one or more members selected from pharmaceutical ingredients suitable for liquid or freeze-dried formulations. The additives include pharmaceutical ingredients suitable for aqueous or non-aqueous injections. Usually, the additive is

selected from conventional pharmaceutical ingredients such as solubilizers, solution adjuvants, suspending agents, buffers (pH regulators), stabilizers and preservatives. In addition, it may be selected from conventional ingredients suitable for preparation of powders for injection, which are used in solution or suspension when administered.

[0121] The oral formulation contains one or more members selected from pharmaceutical ingredients suitable for liquid, freeze-dried and solid formulations. The additives are any pharmaceutical ingredients as long as they are suitable for oral drugs and the intended purposes according to the present invention. Usually, the pharmaceutical additive is selected from conventional pharmaceutical ingredients such as vehicles, binders, disintegrants, lubricants and coating agents. The oral formulations of the present invention include solid and liquid forms. The solid oral preparations include tablets, capsules, granules, fine granules, powders, etc. The liquid oral preparations include syrups, etc.

[0122] Next, the present invention provides pharmaceutical compositions for coadministration with a taxane antineoplastic agent which comprise an effective amount of 2,2'-dithiobis ethane sulfonate to shorten the duration of treatment with the taxane antineoplastic agent. In a more specific embodiment, the present invention provides pharmaceutical compositions for coadministration with a taxane antineoplastic agent which comprise 2,2'-dithiobis ethane sulfonate at a specific wt % to shorten.

[0123] The amount ratio of admixed 2,2'-dithiobis ethane sulfonate in the drug or pharmaceutical composition of the present invention is preferably from 5 to 70 wt %, or more preferably from 10 to 50 wt %.

[0124] Coadministration of the instant drug or pharmaceutical composition in combination with a taxane antineoplastic agent enables us to shorten the duration of taxane antineoplastic agent treatment, though it has been deemed clinically difficult to shorten the duration of taxane treatment because of its safety.

[0125] Thus, when a taxane antineoplastic agent is applied to cancer therapy, it is usually administered once a day. The daily dose for paclitaxel is around 60 to 300 mg/m² (body surface area) and for docetaxel around 30 to 240 mg/m² (body surface area).

[0126] Currently, a taxane antineoplastic agent is administered at the above dose once a day and taxane antineoplastic agent medication then halts for at least 3 to 4 weeks, wherein this medication schedule is set as one course and the course is repeated for cancer therapy (for example, it is noted that the following dosage and administration instructions are present in an approved prescription for paclitaxel injection (TAXOL Injection, Japan):

[0127] Paclitaxel can be infused intravenously over 3 hours at 210 mg/m² (body surface area) once a day followed by halting paclitaxel medication for at least 3 weeks wherein this is defined as one course and the course should be repeated.

[0128] In view of these, the duration of treatment with the said taxane antineoplastic agents will be equal to a long period. For achieving a clinical effect in taxane antineoplastic drug therapy, it is said to be necessary that taxane antineoplastic agent medication should be repeated continu-

ously for at least 2 courses. However, frequently induced disorders of peripheral nerve system (including peripheral neuropathy) often bring taxane antineoplastic agent medication to a halt or lead to a reduced dose whereby it sometimes happens that the expected clinical effect is not so easily achieved.

[0129] When the inventive drugs and pharmaceutical compositions wherein 2,2'-dithiobis ethane sulfonate is contained at the specific parts by weight as aforementioned are coadministered in combination with taxane antineoplastic agents, the drug-induced disorder of peripheral nerve systems (including peripheral neuropathy), particularly the drug-induced paresthetic disorder of peripheral nerve systems, can be alleviated so that it would be possible to maintain patients in a good systemic state. Accordingly, taxane antineoplastic agents can be administered as a next course only after an around one day to 2 week interval, or further only after an interval of about one day to 2 week interval, for suspending drug medication, shorter than the aforementioned conventional 3 to 4 week interval for administering drug medication whereby the duration of taxane treatment can be shortened.

[0130] In such a case, the dose of taxane antineoplastic agents may be in such a level that the anti-tumor effect can be exerted. In other words, it may be less than the aforementioned single: dose level for paclitaxel and docetaxel. More specifically, paclitaxel may be administered at a single dose of around 60 to 300 mg/m² (body surface area) per administration and docetaxel at a single dose of around 30 to 240 mg/m² (body surface area) per administration.

[0131] The interval for administering anticancer drug medication is shortened to around one day to 1.5 weeks, or around, one day to 1 week. As a result, it will be possible to shorten an interval for suspending anticancer drug medication.

[0132] Even when the abovementioned 3 to 4 week interval for suspending anticancer drug medication is adopted, the inventive drugs and pharmaceutical compositions still allow us to continue taxane antineoplastic medication for a longer period exceeding 3 courses minimally required for the achievement of their clinical effect. For the long-term taxane antineoplastic therapy, the course may be repeated at least 4 or more times, or at least 5 or more times, in other cases, at least 6 or more times, and further 7 to 9 times or more.

[0133] These are also supported by the results of the following clinical trials carried out by the present inventors. Thus, as will be mentioned below in Examples, when 2,2'-dithiobis ethane sulfonate is administered, for example at a dose of 8.2 g/m², to patients to whom two species of antineoplastic agents, i.e., paclitaxel and cisplatin, are coadministered, to our surprise, the course can be now repeated up to 9 times. This is far above the assumption under the present circumstance where there is a report that coadministration of paclitaxel with cisplatin tends to increase the neurotoxicity (*J. Clin. Oncol.*, 15(5), 1965, 1997).

[0134] Thus, the present invention also provides drugs for preventing or mitigating taxane anticancer drug-induced disorder of peripheral nerve systems in taxane antineoplastic therapy in combination with platinum analogue antineoplastic therapy which comprises an effective amount of 2,2'-

dithiobis ethane sulfonate. In a more specific embodiment, the present invention provides drugs for preventing or mitigating taxane anticancer drug-induced paresthetic disorder of peripheral nerve systems in taxane antineoplastic therapy in combination with platinum analogue antineoplastic therapy which comprises an effective amount of 2,2'-dithiobis ethane sulfonate. In the coadministration therapy of taxane anticancer drugs in combination with platinum analogue antineoplastic agents, because of the admixture of 2,2'-dithiobis ethane sulfonate, the inventive drugs and pharmaceutical compositions also serve as agents which shorten the duration of treatment with the said antineoplastic agents or increase medication repeats of the said antineoplastic agents. Accordingly, the present invention still provides therapeutic methods using 2,2'-dithiobis ethane sulfonate having the aforementioned functions, drug sets suitable therefore, and further medication sets and methods suitable for not only schedules regarding the drug dose and medication halt but also long-term taxane antineoplastic therapy.

[0135] As such, the above-mentioned 2,2'-dithiobis ethane sulfonate drugs and pharmaceutical compositions allow us to administer taxane antineoplastic agents at shorter intervals than before and therefore are extremely useful in cancer therapy. In addition, even when the conventional dose intervals are adopted, the inventive 2,2'-dithiobis ethane sulfonate drugs and pharmaceutical compositions allow us to administer taxane antineoplastic agents for a longer period in a continuous manner. As a result, the duration of treatment with taxane antineoplastic agents can be shortened.

[0136] The drugs for mitigating the disorder of peripheral nerve systems (including peripheral neuropathy) and pharmaceutical compositions containing a specific amount of 2,2'-dithiobis ethane sulfonate can be coadministered substantially with simultaneous taxane antineoplastic agent administration, or their dosing hours can be staggered as long as they may be allowed to coexist in patient's blood. When the dosing hours are staggered, 2,2'-dithiobis ethane sulfonate may be administered either before or after a taxane antineoplastic agent dose. However, it is preferred that the staggered time difference therebetween is within about 2 hours, and more preferably within 1 hour.

[0137] Pharmaceutically acceptable packs or drug sets (and/or containers or packages) and kits (administration or therapeutic kits) comprising one or more active agents, pharmaceutical preparations, compositions, drugs or agents useful in therapy, of the present invention, are also valuable. Such packs and kits comprising one or more containers filled with one or more effective ingredients or components for the aforementioned drugs or compositions. Examples of such packs and kits are pharmaceutically acceptable packs or kits suitably directed to cancer therapy. Typically, associated with such a single or plural containers can be a notice (attached document) in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products, reflecting approval by the agency of the manufacture, use or sale of the product for human administration. These may include packed products, and further constructs which are constituted via adopting suitable dosage steps, etc. so as to achieve more desirable medical therapy including desired cancer therapy and the like.

[0138] Human clinical trials have been conducted in the United States, Europe and Japan regarding the safety and efficacy of the agents that make up this invention. These trials are ongoing. The following is a summary of the results obtained from early-stage (Phase I) trials in the United States and Japan.

[0139] In the Phase I study in the United States, human patients in Stage I received the following treatment regimen every 3 weeks: a single dose of paclitaxel (175 mg/m²) administered intravenously over 3 hours, pre-cisplatin saline hydration (1000 mL 0.9% NaCl) for 2 hours, followed immediately by a single dose of 2,2'-dithiobis ethane sulfonate (4.1, 8.2, 12.3, 18.4, 27.6 and 41.0 g/m², depending on cohort assignment) administered intravenously over 15 or 30 minutes, a single dose of cisplatin (75 mg/m²) administered intravenously over 1 hour and subsequently post-cisplatin saline hydration (500 cc 0.9% NaCl) for 1 hour.

[0140] Patients in Stage II received sequentially decreasing pre- and post-cisplatin hydration (Levels A to D: 1000/500, 500/250, 250/250, 0/0 mL 0.9% NaCl) with the following treatment regimen every 3 weeks: a single dose of paclitaxel (175 mg/m²) administered intravenously over 3 hours, pre-cisplatin saline hydration from 2 hours to 30 minutes, immediately followed by a single dose of 2,2'-dithiobis ethane sulfonate (18.4 g/m²) administered intravenously over 15 minutes, a single dose of cisplatin (75 mg/m²) administered intravenously over 1 hour and subsequently post-cisplatin saline hydration for 1 hour to 30 minutes.

[0141] A total of 36 patients (22 patients in Stage I and 14 patients in Stage II) with advanced solid tumors have been enrolled and treated in this study at two clinical sites in the United States. A total of 138 treatment courses of BNP7787 with chemotherapy were given to 36 patients giving an average number of 3.8 treatment cycles per patient. A total of 13 patients (36.1%) completed at least five treatment cycles while 5 patients (13.9%) completed at least seven treatment cycles.

[0142] In the Phase I study in Japan, patients received the following treatment regimen every 3 weeks: a single dose of paclitaxel (175 mg/m²) administered intravenously over 3 hours, pre-cisplatin saline hydration for 1 hour, immediately followed by a single dose of 2,2'-dithiobis ethane sulfonate (4.1, 8.2, 12.3, 18.4, 27.6 and 41.0 g/m², depending on cohort assignment) administered intravenously over 30 minutes, a single dose of cisplatin (75 mg/m²) administered intravenously over 1 hour and subsequently post-cisplatin saline hydration for 1.5 hours.

[0143] A total of 19 patients with advanced Non-Small Cell Lung Cancer (NSCLC) have been enrolled and treated in this study at four clinical sites in Japan. Each patient was to receive a total of three treatment cycles during this study. A total of 43 treatment courses of 2,2'-dithiobis ethane sulfonate with chemotherapy were given to 19 patients giving an average of 2.3 treatment cycles per patient. A total of 11 patients (57.9%) completed all three treatment cycles while 8 patients (42.1%) discontinued therapy prior to completing the three treatment cycles.

[0144] The number and percentage of patients who reported neurotoxicity in the Phase I studies compared with historical control data are summarized on the next page. Severity grades were measured according to NCI-CTC standards.

Incidence of Neurotoxicity in US & Japan Phase I Studies Compared with Historical Control all Doses of 2,2'-dithiobis Ethane Sulfonate (4.1 to 41.0 g/m²)

[0145] Number (%) of Patients

Neurotoxicity Grade ¹ (NCI-CTC)	United States (n = 36)	Japan (NSCLC) (n = 19)	Overall (US & Japan) (n = 55)	Historical Control ² (n = 38)
1	8 (22.2)	13 (68.4)	21 (38.2)	11 (29.0)
2	8 (22.2)	1 (5.2)	9 (16.4)	8 (21.0)
3	0 (0.0)	0 (0.0)	0 (0.0)	7 (18.0)
4	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.0)
≥2	8 (22.2)	1 (5.2)	9 (16.4)	16 (42.1)
Overall	16 (44.0)	14 (73.6)	30 (54.5)	27 (71.0)

¹No Grade 3 or 4 events of neurotoxicity were reported in the Phase I studies.

²Treatment regimen = paclitaxel (135 to 175 mg/m²) administered IV over 3 hours followed by cisplatin (75 mg/m²) administered IV over 30 minutes in patients with gynecologic cancer (Connelly et al., Gyn. Onc. 62: 166-168;1996).

[0146] Overall, peripheral neuropathy, such as numbness, paresthesia or tingling, was reported in 54.5% of patients (30 patients, all severities) in the Phase I studies. The majority of neurotoxicity events experienced was mild in severity where 38.2% of patients (21 patients) reported Grade 1 neurotoxicity. A few patients experienced neurotoxicity events that were moderate in severity where 16.4% of patients (9 patients) reported Grade 2 peripheral neuropathy. No patient experienced Grade 3 or 4 neurotoxicity including, patients who received up to 9 cycles of chemotherapy. Notably, peripheral neuropathy was not a dose limiting toxicity when 2,2'-dithiobis ethane sulfonate was administered concurrently with paclitaxel and cisplatin chemotherapy.

[0147] Based on historical control data, the expected overall incidence for neurotoxicity is 71.0% and the incidence of moderate to severe (>Grade 2) neurotoxicity is 42.1%. Results from the Phase I studies showed a marked reduction in both the overall incidence of neurotoxicity and the incidence of moderate to severe (≥Grade 2) neurotoxicity. As can be noted from the table, the overall incidence for neurotoxicity was 54.5% in the Phase I studies compared with 71.0% from historical control data and the incidence for moderate to severe (≥Grade 2) neurotoxicity was 16.4% in the Phase I studies compared with 42.1% from historical control data. The results indicate that the concurrent administration of 2,2'-dithiobis ethane sulfonate with cisplatin and paclitaxel chemotherapy decreases the incidence of neurotoxicity.

[0148] The following are examples of the present invention, which are provided only for illustrative purposes, and not to limit the scope of the present invention.

EXAMPLE 1

Inhibiting Efficacy of 2,2'-dithiobis Ethane Sulfonate Against Paclitaxel-Induced Abnormal Thermoesthesia

<Methods >

[0149] Paclitaxel was intravenously administered at a dose of 6 mg/kg once daily to female Wistar rats (8 rats per group)

(the initial dosage date was defined as day 0). Treatment was repeated five times every other day.

[0150] The efficacy of 2,2'-dithiobis ethane sulfonate on the abnormal thermoesthesia occurring in response to the paclitaxel therapy was assessed using, as an index, a latent period for pseudo pain reactions. The pseudo pain reaction related latent period is defined in terms of seconds counting from the initial point at which the rat hind limb was dipped in a hot water bath of 45° C. until the point at which the rat showed an avoidance reflex. Each pseudo pain reaction-related latent period was measured on the day before the initial paclitaxel dosage (day -1, pretreatment), and daily for three days from the next day after the final paclitaxel dosage (from days 9 to 11, post-treatment), i.e., totally four times.

[0151] 2,2'-dithiobis ethane sulfonate was, dissolved in water for injection to make its concentration 200 mg/ml upon use and the 2,2'-dithiobis ethane sulfonate solution thus prepared was intravenously administered at the dose of 500 mg/kg or 1,000 mg/kg immediately before the paclitaxel administration.

<Results >

[0152] As will be apparent from Table 1, for groups receiving paclitaxel alone, the latent period prior to the initiation of paclitaxel administration (pretreatment) was 9.4±1.0 seconds while the latent periods on days 9, 10 and 11 post-treatment were 18.9±1.4, 19.9±2.2 and 19.4±2.4 seconds, respectively. As compared with the latent periods simultaneously measured with regard to control groups, it is noted that such paclitaxel administration-related latent periods are significantly elongated (p<0.01: student's t-test or Man-Whitney U-test).

[0153] In contrast, there was noted a suppressing tendency as a whole for a latent period in groups receiving 500 mg/kg or 1000 mg/kg of 2,2'-dithiobis ethane sulfonate in advance. In groups receiving 1000 mg/kg of 2,2'-dithiobis ethane sulfonate on day 9, significant suppressing effects to elongate the latent period were noted (p<0.05; Dunnet test).

[0154] From the results, it is apparent that 2,2'-dithiobis ethane sulfonate mitigates effectively paclitaxel-induced abnormal thermoesthesia.

TABLE 1

Dose (mg/kg) 2,2'-dithiobis ethane sulfonate/	Latent Period (sec) for Thermal Stimuli at 45° C. (Inhibition Rate %)			
	Pretreatment	Post-Treatment		
Paclitaxel	Day-1	Day 9	Day 10	Day 11
PS/Solvent* (Control Groups)	9.7 ± 1.0	9.9 ± 0.9	9.9 ± 1.2	9.6 ± 0.8
PS/6 (Paclitaxel Alone)	9.4 ± 1.0	18.9 ± 1.4	19.9 ± 2.2	19.4 ± 2.4
500/6	9.5 ± 0.8	17.6 ± 1.5 (17.8)	18.1 ± 2.2 (18.0)	17.5 ± 2.2 (19.4)
1,000/6	9.7 ± 1.0	15.0 ± 1.0 (43.3)	16.1 ± 2.5 (38.0)	14.4 ± 1.4 (51.0)

*Solvent (Cremophor® EL:Ethanol:PS = 1:1:46)
PS = Physiological Saline

EXAMPLE 2

[0155] A 34-year-old female patient with adenocarcinoma of unknown origin presented with a pituitary mass and supraclavicular and mediastinal lymph nodes. She received the following treatment regimen every 3 weeks: a single dose of paclitaxel (175 mg/m²) administered IV over 3 hours, pre-cisplatin saline hydration (500 mL 0.9% NaCl) for 1 hour, a single dose of BNP7787 (18.4 g/m²) administered IV over 15 minutes, immediately followed by a single dose of cisplatin (75 mg/m²) administered IV over 1 hour and subsequently post-cisplatin saline hydration (250 mL 0.9% NaCl) for 30 minutes. The patient received a total of six cycles of study treatment and experienced peripheral neuropathy (NCI-CTC Grade 2) during Cycles 4 through 6. The patient experienced a complete response after Cycle 2, which was confirmed after Cycles 4 and 6. The patient discontinued study treatment due to the complete response and remained on study for follow-up.

EXAMPLE 3

[0156] A 43-year-old female patient with adenocarcinoma of gastric origin received the following treatment regimen every 3 weeks: a single dose of paclitaxel (175 mg/m²) administered IV over 3 hours, pre-cisplatin saline hydration (500 mL 0.9% NaCl) for 1 hour, a single dose of BNP7787 (18.4 g/m²) administered IV over 15 minutes, immediately followed by a single dose of cisplatin (75 mg/m²) administered IV over 1 hour and subsequently post-cisplatin saline hydration (250 mL 0.9% NaCl) for 30 minutes. The patient received a total of five cycles of study treatment with no peripheral neuropathy. The patient experienced stable disease from Cycles 2 through 4 and was subsequently discontinued from the study due to progressive disease following Cycle 5.

EXAMPLE 4

[0157] A 46-year-old female patient with adenocarcinoma of unknown origin presented with retroperitoneal and lung masses. She received the following treatment regimen every 3 weeks: a single dose of paclitaxel (175 mg/m²) administered IV over 3 hours, pre-cisplatin saline hydration (250 mL 0.9% NaCl) for 30 minutes, a single dose of BNP7787 (18.4 g/m²) administered IV over 15 minutes, immediately followed by a single dose of cisplatin (75 mg/m²) administered IV over 1 hour and subsequently post-cisplatin saline hydration (250 mL 0.9% NaCl) for 30 minutes. The patient received a total of six cycles of study treatment and experienced Grade 1 numbness and tingling (peripheral neuropathy) beginning Day 2 of Cycle 1 which resolved on Day 5. The patient again experienced Grade 1 peripheral neuropathy during Cycle 4. The patient experienced a partial response after Cycle 2 and a complete response after Cycle 6. The patient discontinued study treatment due to the complete response and remained on study for follow-up.

EXAMPLE 5

[0158] A 69-year-old male patient with adenocarcinoma of the lung received the following treatment regimen every 3 weeks: a single dose of paclitaxel (175 mg/m²) administered IV over 3 hours, pre-cisplatin saline hydration for 1 hour, immediately followed by a single dose of BNP7787 (18.4 g/m²) administered IV over 30 minutes, a single dose of cisplatin (75 mg/m²) administered IV over 1 hour and subsequently post-cisplatin saline hydration for 1.5 hours. The patient received a total of 3 cycles of study treatment

and experienced no peripheral neurotoxicity. The patient had a partial response after Cycles 2 and 3 and was discontinued from the study after completing the pre-defined number of treatment cycles.

EXAMPLE 6

[0159] A 52-year-old female patient with adenocarcinoma of the lung received the following treatment regimen every 3 weeks: a single dose of paclitaxel (175 mg/m²) administered IV over 3 hours, pre-cisplatin saline hydration for 1 hour, immediately followed by a single dose of BNP7787 (18.4 g/m²) administered IV over 30 minutes, a single dose of cisplatin (75 mg/m²) administered IV over 1 hour and subsequently post-cisplatin saline hydration for 1.5 hours. The patient received a total of 3 cycles of study treatment and experienced Grade 1 peripheral neurotoxicity beginning on Day 6 of Cycle 3, which resolved on Day 20 of Cycle 3. The patient had a partial response after Cycles 2 and 3 and was discontinued from the study after completing the pre-defined number of treatment cycles.

EXAMPLE 7

[0160] A 53-year-old male patient with large cell carcinoma of the lung received the following treatment regimen every 3 weeks: a single dose of paclitaxel (175 mg/m²) administered IV over 3 hours, pre-cisplatin saline hydration for 1 hour, immediately followed by a single dose of BNP7787 (18.4 g/m²) administered IV over 30 minutes, a single dose of cisplatin (75 mg/m²) administered IV over 1 hour and subsequently post-cisplatin saline hydration for 1.5 hours. The patient received a total of 3 cycles of study treatment and experienced Grade 1 peripheral neurotoxicity beginning on Day 5 of Cycle 2. The patient had stable disease and was discontinued from the study after completing the pre-defined number of treatment cycles.

What is claimed is:

1. A drug for preventing and mitigating taxane antineoplastic agent induced toxic disorder of peripheral nerve systems, which comprises an effective amount of 2,2'-dithiobis ethane sulfonate.
2. A drug for preventing and mitigating the taxane antineoplastic agent-induced paresthetic disorder of peripheral nerve systems, which comprises an effective amount of 2,2'-dithiobis ethane sulfonate.
3. A drug for shortening the duration of treatment with a taxane antineoplastic agent in taxane antineoplastic therapy, which comprises an effective amount of 2,2'-dithiobis ethane sulfonate.
4. The drug according to claim 3 in which, the duration of treatment consists of a period for medication of a taxane antineoplastic agent and an interval for suspending taxane antineoplastic agent medication.
5. The drug according to claim 4 in which the duration of treatment comprises at least 3 continuous courses wherein each course consists of a period for medication of a taxane antineoplastic agent and an interval for suspending taxane antineoplastic agent medication.
6. A drug for shortening an interval for suspending medication of a taxane antineoplastic agent in taxane antineoplastic therapy, which comprises an effective amount of 2,2'-dithiobis ethane sulfonate.
7. The drug according to any of claims 4 to 6 in which the interval for suspending taxane antineoplastic agent medication is from one day to 2.5 weeks.

8. The drug according to any of claims 4 to 6 in which the interval for suspending taxane antineoplastic agent medication is from one day to 2 weeks.

9. The drug according to any of claims 4 to 6 in which the interval for suspending taxane antineoplastic agent medication is from one day to 1.5 weeks.

10. The drug according to any of claims 4 to 6 in which the interval for suspending taxane antineoplastic agent medication is from one day to 1 week.

11. A drug for increasing the number of courses for treatment with a taxane antineoplastic agent in taxane antineoplastic therapy, which comprises an effective amount of 2,2'-dithiobis ethane sulfonate.

12. The drug according to claim 11 in which the treatment comprises 4 or more courses.

13. The drug according to claim 11 in which the taxane treatment comprises 5 or more courses.

14. The drug according to claim 11 in which the taxane treatment comprises 6 or more courses.

15. The drug according to claim 11 in which the taxane treatment comprises 7 or more courses.

16. The drug according to claim 11 in which the taxane treatment comprises 8 or more courses.

17. The drug according to claim 11 in which the taxane treatment comprises 9 or more courses.

18. The drug according to any of claims 11 to 17 in which said courses are continuous.

19. A drug for mitigating taxane antineoplastic agent-related adverse actions, which comprises plural or all members selected from elements as set forth in any of claims 1 to 18.

20. The drug according to any of claims 1 to 19 in which 2,2'-dithiobis ethane sulfonate is admixed at 5 to 70 wt % per total pharmaceutical preparation.

21. The drug according to any of claims 1 to 19 in which 2,2'-dithiobis ethane sulfonate is admixed at 15 to 50 wt %.

22. The drug according to any of claims 1 to 21 in which the amount of admixed 2,2'-dithiobis ethane sulfonate is for administering 4.1 to 41.0 g/m² (body surface area) per day.

23. The drug according to any of claims 1 to 22, which is for intravenous or oral administration routes.

24. The drug according to claim 23 in which the drug for intravenous or oral administration routes is in any of liquid, freeze-dried and solid forms.

25. The drug according to any of claims 1 to 24 in which the taxane antineoplastic agent is paclitaxel.

26. The drug according to any of claims 1 to 24 in which the taxane antineoplastic agent is docetaxel.

27. The drug according to any of claims 1 to 26, which is for taxane antineoplastic drug therapy in combination with platinum analogue antineoplastic drug therapy.

28. The drug according to claim 27 in which the platinum analogue antineoplastic agent is cisplatin.

29. The drug according to claim 27 in which the platinum analogue antineoplastic agent is carboplatin.

30. A pharmaceutical composition for coadministration with a taxane antineoplastic agent, which comprises an effective amount of 2,2'-dithiobis ethane sulfonate in order to mitigate the taxane antineoplastic agent-induced disorder of peripheral nerve systems.

31. A pharmaceutical composition or coadministration with a taxane antineoplastic agent, which comprises an effective amount of 2,2'-dithiobis ethane sulfonate in order to mitigate the taxane antineoplastic agent-induced paresthetic disorder of peripheral nerve systems.

32. A pharmaceutical composition for coadministration with a taxane antineoplastic agent, which comprises an

effective amount of 2,2'-dithiobis ethane sulfonate in order to shorten the duration of treatment with the taxane antineoplastic agent in taxane antineoplastic therapy.

33. A pharmaceutical composition for administration with a taxane antineoplastic agent, which comprises an effective amount of 2,2'-dithiobis ethane sulfonate in order to shorten an interval for suspending medication with the taxane antineoplastic agent in taxane antineoplastic therapy.

34. A pharmaceutical composition for coadministration with a taxane antineoplastic agent, which comprises an effective amount of 2,2'-dithiobis ethane sulfonate in order to increase the number of courses for treatment with a taxane antineoplastic agent in taxane antineoplastic therapy.

35. A pharmaceutical composition for coadministration with a taxane antineoplastic agent, which comprises an effective amount of 2,2'-dithiobis ethane sulfonate in order to exert plural or all actions selected from the group consisting of

(1) a mitigating activity against the taxane antineoplastic agent-related disorder of peripheral nerve systems,

(2) a mitigating activity against the taxane antineoplastic agent-related paresthetic disorder of peripheral nerve systems,

(3) a shortening activity on the duration of taxane antineoplastic agent treatment,

(4) a shortening activity on the interval for suspending taxane antineoplastic agent, medication during taxane antineoplastic drug therapy, and

(5) an increasing activity on the number of courses for taxane antineoplastic agent medication during taxane antineoplastic drug therapy.

36. The pharmaceutical composition according to any of claims 30 to 35 in which 2,2'-dithiobis ethane sulfonate is admixed at 5 to 70 wt % per total pharmaceutical preparation.

37. The of claims 30 to 35 in which 2,2'-dithiobis ethane sulfonate is admixed at 10 to 50 wt %.

38. The pharmaceutical composition according to any of claims 30 to 35 in which the amount of admixed 2,2'-dithiobis ethane sulfonate is for administering 4.1 to 80.0 g/m² (body surface area).

39. The pharmaceutical composition according to any of claims 30 to 38, which is for intravenous or oral administration routes.

40. The pharmaceutical composition according to claim 39 in which the drug for intravenous or oral administration routes is in any of liquid, freeze-dried and solid forms.

41. The pharmaceutical composition according to any of claims 30 to 40 in which the taxane antineoplastic agent is paclitaxel.

42. The pharmaceutical composition according to any of claims 30 to 40 in which the taxane antineoplastic agent is docetaxel.

43. The pharmaceutical composition according to any of claims 30 to 42, which is for taxane antineoplastic drug therapy in combination with platinum analogue antineoplastic drug therapy.

44. The pharmaceutical composition according to claim 43 in which the platinum analogue antineoplastic agent is cisplatin.

45. The pharmaceutical composition according to claim 43 in which the platinum analogue antineoplastic agent is carboplatin.

46. A drug comprising an effective amount of 2,2'-dithiobis ethane sulfonate for coadministration with a taxane antineoplastic agent in a form of packs or formulations in order to allow the following:

- (1) one course is set to include the following administration schedules:

the taxane antineoplastic agent is administered once a day wherein the antineoplastic agent is administered at one day to 5 week intervals, and

2,2'-dithiobis ethane sulfonate is administered on the same date as the antineoplastic agent is administered, and

- (2) the medication is repeated for at least 4 courses preferably 7 or more courses.

47. The drug according to claim 46 in which the weight ratio of 2,2'-dithiobis ethane sulfonate to antineoplastic agent is from 1:10 to 1:2500.

48. The drug according to claim 46 in which the dose of 2,2'-dithiobis ethane sulfonate is from 4.1 to 41.0 g/m²(body surface area) per day.

49. The drug according to any of claims 46 to 48 in which the single dose of the taxane antineoplastic agent is from 60 to 300 mg/m² (body surface area) per day for paclitaxel or from 30 to 240 mg/m² (body surface area) per day for docetaxel.

50. The drug according to any of claims 46 to 49 in, which the course is repeated at least 8 or more times.

51. The drug according to any of claims 46 to 50 in which the antineoplastic agents are administered at intervals of (a) one day to 4 weeks, (b) one day to 3 weeks, or (c) one day to 2 weeks.

52. The drug according to any of claims 46 to 50 in which the antineoplastic agent is administered at an interval of one day to 1.5 week.

53. The drug according to any of claims 46 to 52, which exert at least one, plural, or all actions selected from the group consisting of

- (1) a mitigating activity against the taxane antineoplastic agent-related disorder of peripheral nerve systems,
- (2) a mitigating activity against the taxane antineoplastic agent-related paresthetic disorder of peripheral nerve systems,
- (3) a shortening activity on the duration of taxane antineoplastic agent treatment,
- (4) a shortening activity on the interval for suspending taxane antineoplastic agent medication during taxane antineoplastic drug therapy, and
- (5) an increasing activity on the number of courses for taxane antineoplastic agent medication during taxane antineoplastic drug therapy.

54. A drug comprising an effective amount of 2,2'-dithiobis ethane sulfonate for coadministration with a taxane antineoplastic agent in a form of packs or formulations in order to allow the following:

- (1) one course is set to include the following administration schedules:

the taxane antineoplastic agent is administered once a day as well as a platinum analogue antineoplastic

agent is administered on the same date as the taxane antineoplastic agent is administered wherein the antineoplastic agents are administered at 0.5 to 6, week intervals, and

2,2'-dithiobis ethane sulfonate is administered on the same date as the antineoplastic agents are administered; and

- (2) the medication is repeated for at least 4 courses, preferably 7 or more courses.

55. The drug according to claim 54 in which the weight ratio of 2,2'-dithiobis ethane sulfonate to taxane antineoplastic agent is from 1:10 to 1:2500.

56. The drug according to claim 54 in which the dose of 2,2'-dithiobis ethane sulfonate is from 4.1 to 80.0 g/m² (body surface area).

57. The drug according to any of claims 54 to 56 in which the single dose of the taxane antineoplastic agent is from 60 to 300 mg/m² (body surface area) per day for paclitaxel or from 30 to 240 mg/m² (body surface area) per day for docetaxel.

58. The according to all of claims 54 to 56 in which the platinum analogue antineoplastic agent is cisplatin or carboplatin.

59. The drug according to any of claims 54 to 58 in which the course is repeated at least 8 or more times.

60. The drug according to any of claims 54 to 59 in which the antineoplastic agents are administered at intervals of (a) one day to 5 weeks, (b) one day to 4 weeks, or (c) one day to 3 weeks.

61. The drug according to any of claims 54 to 59 in which the antineoplastic agent is administered at an interval of 2.5 to 5 weeks.

62. The drug according to any of claims 54 to 61 which exerts at least one, plural or all actions selected from the group consisting of

- (1) a preventing or mitigating activity against the taxane antineoplastic agent-related disorder of peripheral nerve systems,
- (2) a preventing or mitigating activity against the taxane antineoplastic agent-related paresthetic disorder of peripheral nerve systems,
- (3) a shortening activity on the duration of taxane antineoplastic agent treatment,
- (4) a shortening activity of the interval for suspending taxane antineoplastic agent medication during taxane antineoplastic drug therapy, and
- (5) an increasing activity on the number of courses for taxane antineoplastic agent medication during taxane antineoplastic drug therapy.

63. The drug according to any of claims 46 to 62, which serves as an agent for mitigating taxane antineoplastic agent-related adverse actions.

64. The pharmaceutical composition according to any of claims 30 to 45 in which 2,2'-dithiobis ethane sulfonate is co-administrable as a medication set in combination with taxane antineoplastic agent medication.

65. The pharmaceutical composition according to claim 64 in which a platinum analogue antineoplastic agent is co-administrable as a medication set.

* * * * *